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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
KAM, CHIH MIN

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 09/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/926,391	SHIOJIRI ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1/16/02* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. In the preliminary amendment filed January 8, 2002, claims 1-11 have been amended, and new claims 12-19 have been added; In the second preliminary amendment filed June 21, 2002, claim 1 has been amended. Therefore claims 1-19 are examined.

Claim Objections

2. Claim 1 is objected to because it recites a misspelled word "quanidino".

3. Claim 10 is objected to because of the use of the term "at least peptide derivative or salt thereof", the word "one" should be inserted after "at least".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 5-7 and 12-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a melanocyte-stimulating hormone inhibitory composition which comprises D-2-naphthylalanyl-Arg-LeuNH_2 as an active ingredient exhibiting an IC50 for cAMP production less than 100 nM, or, a whitening agent or a cosmetic preparation comprises the composition, does not reasonably provide enablement for a melanocyte-stimulating hormone inhibitory composition which comprises a melanocyte-stimulating hormone inhibiting compound as an active ingredient exhibiting an IC50 for cAMP production less than 100 nM, where the melanocyte-stimulating hormone inhibiting compound is not defined; a whitening agent, an immunofunction controlling agent, an appetite controlling agent or a cosmetic preparation comprises the composition. The specification does not enable a person skilled in the art to which

it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 5-7 and 12-15 are directed to a melanocyte-stimulating hormone inhibitory composition which comprises a melanocyte-stimulating hormone inhibiting compound as an active ingredient exhibiting an IC50 for cAMP production less than 100 nM (claims 5-7); a whitening agent (claim 12), an immunofunction controlling agent (claim 13), an appetite controlling agent (claim 14) or a cosmetic preparation comprises the composition (claim 15). The specification, however, only discloses cursory conclusions (pages 7-8) without data supporting the findings, which state that the present invention relates to a melanocyte-stimulating hormone inhibitory composition which comprises a melanocyte-stimulating hormone inhibiting compound and are not limited to the peptides of formula (I) as an active ingredient exhibiting an IC50 for cAMP production less than 100 nM, and a whitening agent, an immunofunction controlling agent, an appetite controlling agent or a cosmetic preparation comprises the melanocyte-stimulating hormone inhibitory composition. There are no indicia that the present application enables the full scope in view of the melanocyte-stimulating hormone inhibiting compound as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the presence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding the melanocyte-stimulating hormone inhibiting compound, and use of the compound as whitening agent, an immunofunction controlling agent, an appetite controlling agent or a cosmetic preparation, which are not adequately described or demonstrated in the specification.

(2). The presence or absence of working examples:

The specification indicates measurement of IC50 of cAMP production, suppression of the melanin formation caused by melanocytes, stability during storage, inhibition of melanocyte-stimulating hormone in vivo (suppression of pigmentation in animal model) for D-2-naphthylalanyl-Arg-LeuNH$_2$, D-1-naphthylalanyl-Arg-LeuNH$_2$, L-1-naphthylalanyl-Arg-LeuNH$_2$, and D-Trp-Arg-NH$_2$, and cosmetic preparation comprising the melanocyte-stimulating hormone inhibitory composition have been performed (Examples, pages 27-43), it appears only D-2-naphthylalanyl-Arg-LeuNH$_2$ is effective in inhibiting melanocyte-stimulating hormone in vitro and in vivo. There are no other working examples indicating the claimed variants.

(3). The state of the prior art and relative skill of those in the art:

The prior art (references at pages 2-3 of the specification) teach several known melanocyte-stimulating hormone inhibitors such as D-Trp-Arg-Leu-NH$_2$ which have undesired effects or stability problem during storage, while the specification indicates the claimed peptides have inhibitory effect against melanocyte-stimulating hormone and pigmentation. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on identities of various melanocyte-stimulating

hormone inhibitors, and the effects of these inhibitors to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass many inhibitor variants and the effects of these various compounds as whitening agents, immunofunction controlling agents, appetite controlling agents or cosmetic preparation are not described in the specification, the invention is highly unpredictable regarding the effects of these inhibitors, e.g., only D-2-naphthylalanyl-Arg-$LeuNH_2$ is effective in inhibiting melanocyte-stimulating hormone in vitro and in vivo, while the other two peptides, D-1-naphthylalanyl-Arg-$LeuNH_2$, L-1-naphthylalanyl-Arg-$LeuNH_2$ are not effective in vitro.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a melanocyte-stimulating hormone inhibitory composition which comprises a melanocyte-stimulating hormone inhibiting compound as an active ingredient exhibiting an IC50 for cAMP production less than 100 nM; or, a whitening agent, an immunofunction controlling agent, an appetite controlling agent or a cosmetic preparation comprises the composition. The specification indicates peptides of formula (I) such as D-2-naphthylalanyl-Arg-$LeuNH_2$, D-1-naphthylalanyl-Arg-$LeuNH_2$, L-1-naphthylalanyl-Arg-$LeuNH_2$, and D-Trp-Arg-NH_2 inhibit cAMP production and suppress melanin formation caused by melanocytes, and D-2-naphthylalanyl-Arg-$LeuNH_2$ is effective in inhibiting melanocyte-stimulating hormone in vitro and in vivo and can be used as whitening agent and in a cosmetic preparation (Examples, pages 27-43). However, the specification has not identified various melanocyte-stimulating hormone inhibiting compounds besides D-2-naphthylalanyl-Arg-

$LeuNH_2$ which exhibits an IC50 for cAMP production less than 100 nM, nor has demonstrated the use of various melanocyte-stimulating hormone inhibiting compounds as a whitening agent, an immunofunction controlling agent, an appetite controlling agent or a cosmetic preparation. There are no working examples indicating the making and use of various melanocyte-stimulating hormone inhibiting compounds. Furthermore, there is no *in vitro* or *in vivo* data indicating compounds different from D-2-naphthylalanyl-Arg-$LeuNH_2$ are effective inhibitors for melanocyte-stimulating hormone. Therefore, it is necessary to have additional guidance on the identities of various melanocyte-stimulating hormone inhibiting compounds, and to carry out further experimentation to assess the in vivo effects of these compounds.

(6). Nature of the Invention

The scope of the claims includes many structural variants, however the specification has not demonstrated the use and the effects of these peptide variants in inhibiting melanocyte-stimulating hormone. Thus, the disclosure is not enabling for reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed variants, and the teaching in the specification is limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effect of the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claims 1-4, 8-11 and 16-19 are indefinite because of the use of the term "di- or tripeptide derivative", "peptide derivative" or "may have". The term "di- or tripeptide derivative", "peptide derivative" or "may have" renders the claim indefinite, it is not clear how different the peptide derivative is from the parent peptide, deletion of the term "derivative" is suggested. It is also not clear whether the limitations following the term "may have" are part of the claimed invention. Claims 2-4, 8-11 and 16-19 are included in the rejection because they are dependent on rejected claims and do not correct the deficiency of the claim from which they depend.

7. Claims 5-7 and 12-15 are indefinite because of the use of the term "cAMP". The term "cAMP" renders the claim indefinite, it is not clear what term "cAMP" means. A fully spelled out word should be indicated at the first occurrence.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 2, 4, 8-11 and 16-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Matsueda *et al.* (U. S. Patent 4,548,936, October 1985).

Matsueda *et al* teach a renin inhibitor having the structure of formula (I), e.g., N-benzyloxycarbonyl-3-(1-naphthyl)-L-alanyl-L-histdyl-L-leucinol (compound 14, column 9;

Example 14) and 3-(1-naphthyl)-L-alanyl-L-histdyl-L-leucinol dihydrobromide (compound 22, column 10, Example 22; claims 1, 2 and 4). These compounds can be formulated with a pharmaceutically acceptable carrier or diluent (column 13, lines 38-50), which meet the criteria of claims 8-11 and 16-19, because these compounds have the same structures as peptides of formula (I) of the claimed invention, thus they would be expected to have melanocyte-stimulating hormone inhibitory activity. Furthermore, the reference indicates these compounds are prepared as an active ingredient of a composition for administration, and the claims merely recites a whitening agent, an immunofunction controlling agent, an appetite controlling agent or a cosmetic preparation comprising the peptide of formula (I) as active ingredient, therefore, claims 8-11 and 16-19 are anticipated by the reference.

9. Claims 1, 2, 4, 8-11 and 16-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Saika *et al.* (WO/95/12611).

Saika *et al* teach an endothelin receptor antagonist having the structure of formula (I), e.g., N-(2-naphthyl)-N-methyl-D-phenylalanyl-L-tryptophan (Example 21, page 50; claims 1, 2 and 4). This compound can be formulated with a pharmaceutically acceptable carrier or diluent (page 39, paragraphs 3 and 4), which meet the criteria of claims 8-11 and 16-19, because this compound has the same structure as peptides of formula (I) of the claimed invention, thus it would be expected to have melanocyte-stimulating hormone inhibitory activity. Furthermore, the reference indicates the compound is prepared as an active ingredient of a composition for administration, and the claims merely recites a whitening agent, an immunofunction controlling agent, an appetite controlling agent or a cosmetic preparation comprising the peptide of formula (I) as active ingredient, therefore, claims 8-11 and 16-19 are anticipated by the reference.

10. Claims 1, 2 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Etzkorn *et al.* (J. Am. Chem Soc. 116, 10412-10425 (1994)).

Etzkorn *et al* teach tendamistat mimics such as Ac-Nap-Arg-Tyr-OMe (compound 17, page 10416; claims 1, 2 and 4).

Conclusion

11. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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September 17, 2003

Christopher S. Low